HEART REVIEW

Prognosis of stable angina pectoris: why we need larger population studies with higher endpoint resolution

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The prognosis of angina was described as ''"unhappy'' by the Framingham investigators and as little different from that of 1-year survivors of acute myocardial infarction. Yet recent clinical trials now report that angina has a good prognosis with adverse outcomes reduced to ''normal levels''. These disparate prognostic assessments may not be incompatible, applying as they do to population cohorts (Framingham) and selected participants in clinical trials. Comparisons between studies are further complicated by the absence of agreed case definitions for stable angina (contrast this with acute coronary syndromes). Our recent data show that for patients with recent onset symptoms attending chest pain clinics, angina remains a high-risk diagnosis and although many patients receive symptomatic benefit from revascularisation, prognosis is usually unaffected. This leaves little room for complacency and, with angina the commonest initial manifestation of coronary artery disease, there is the opportunity for early detection, risk stratification and treatment to modify outcomes. Meanwhile, larger population-based studies are needed to define the patient journey from earliest presentation through the various syndrome transitions to coronary or noncardiac death in order to increase understanding of the aetiological and prognostic differences between the different coronary disease phenotypes.

> ''There is nothing more urgent in clinical medicine than to understand the prognosis of angina.'' Sir James MacKenzie[1]

''Chronic stable angina? We don't see it any more round here'' (an interventional cardiologist, ca 2006). That may be the perception among interventionists, but angina has not gone away.[2] Indeed, it remains the most common initial symptom of coronary heart disease (CHD).[3] Misconceptions about the continuing importance of angina are driven largely by the success of revascularisation in producing short-term symptom relief, although this is not associated with survival benefit. Encouraging results from recent trials of medical treatment have also contributed to the downplaying of angina, with investigators concluding that angina has a good prognosis with adverse outcomes reduced to normal levels.[4 5] These trials have been groundbreaking in terms of their size—remarkably, these are the first trials of medical management of angina powered to detect endpoint differences—and the contribution they have made to contemporary management. However, they mostly recruited white patients from secondary and tertiary centres who were most typically men, most of whom had previous myocardial infarction (MI), and many after the revascularisation procedures.[5–7] At a time when angina is being increasingly diagnosed in primary care populations,[8] we need to know whether the optimistic prognostic assertions of the trialists can be generalised to incident cases within the community—a group that hitherto has received little attention from researchers.

POPULATION-BASED COHORT STUDIES

Not all persons who develop angina seek medical care and of those who do, not all receive a diagnosis.[9] Patients who are diagnosed with angina embark upon a journey of referral, investigation and treatment, with large international variation in the proportion that ultimately undergoes revascularisation.[10] Estimates of future risk of adverse health outcomes (prognosis) can be revised at each stage of this journey, but until recently most reports have originated from the apex of the population pyramid as in figure 1. It is from here that the intensively treated participants, a group of survivors in whom rates of adverse cardiovascular outcomes are very low, in randomised trials are selected. Although the geometry of the pyramid—the proportion ascending to the next level—will depend on the healthcare system and public awareness, its existence is ubiquitous. Selection at each stage involves a complex interaction of pathophysiological factors (patients with more sickness may be more or less likely to be referred) and the quality of healthcare, including inequalities in access.

FRAMINGHAM EXPERIENCE

What is the prognosis of incident angina, as represented by those cases at the base of the pyramid? A glimpse of the more eventful course experienced by this group was provided by the Framingham investigators, who reported 10-year mortality rates of about 40% for men aged >50 years and women aged >60 years.[11] In concluding that ''the lot of the angina victim is not a happy one'', the Framingham investigators drew comparison with 1 year survivors of acute MI for whom long-term all-cause mortality was almost identical. The contrasting features of the Framingham cohort and the participants in recent trials have various explanations, not least the historical context of the Framingham study, but they remind us that caution is needed in interpreting

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction

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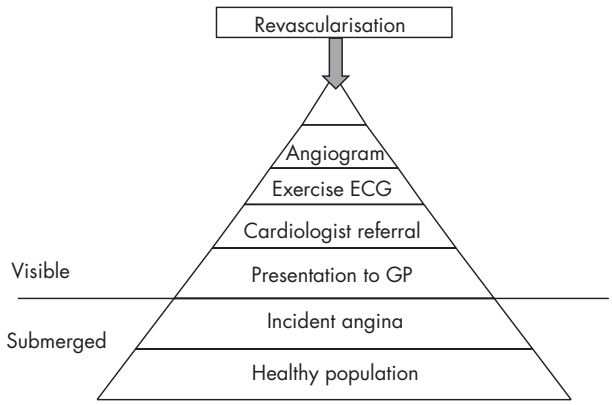

Figure 1 Population pyramid of referral and investigation in stable angina. GP, general practitioner.

outcome data in clinical trials that were designed to examine treatment effects in selected coronary populations, not prognosis in incident cases of angina. The original Framingham report appeared over 30 years ago, but in a 1993 update,[12] the mortality for men with incident angina remained undiminished, although there was some apparent improvement for women.

LACK OF POPULATION STUDIES OF ANGINA INCIDENCE

The attention of epidemiologists has been largely focused on MI and there have been few population studies of incident angina. Indeed, researchers have seen exclusion of angina from their studies as a virtue, regarding it as too soft an end point compared with the conventional aggregate of MI and coronary death. Numerous studies have reported that prevalent angina confers an increased risk of coronary and all-cause mortality in women and men and up to their 80s.[13–15] In 1988, the Gothenburg investigators[16] reported that men with a clinical diagnosis of angina but no history of MI had a 14.1% incidence of fatal and non-fatal coronary events during 7.3 years of follow-up, which was 29.4% in men with angina and previous MI. Taken together, these population-based prognostic data from Framingham and Gothenburg studies describe angina as a high-risk diagnosis in contrast to the more recent data from clinical trials.

CLINICAL EPIDEMIOLOGY FOR THE WHOLE COUNTRY

A problem with population-based studies is that they generate too few cases of angina on which to base reliable estimates of risk, particularly in women, the Framingham angina cohort comprising only 80 women. In countries with well-developed primary care, such as the UK, >95% of citizens are registered with a general practitioner and >90% of adults consult within a 2-year period. Such primary care populations may therefore be more representative of the general population than conventional cohort studies in which response rates seldom exceed 60%.[17]

Recently, in Finland, primary care electronic records for the whole country—linked with census, hospitalisation and mortality data—have permitted estimation of the annual incidence of angina calculated as the ratio of the average number of new

Age group (year)	Sex	Observed/ expected deaths	SMR (95% CI)	p Value for interaction
Nitrate angina				
45–54	Women	18/3	5.19 (3.08 to 8.20)	0.45
	Men	127/31	4.14 (3.46 to 4.90)	
55–64	Women	120/45	2.65 (2.22 to 3.17)	0.14
	Men	356/158	2.25 (2.03 to 2.50)	
65–74	Women	587/418	1.40 (1.29 to 1.52)	0.005
	Men	976/599	1.63 (1.53 to 1.74)	
75–84	Women	1630/1392	1.17 (1.12 to 1.23)	0.05
	Men	1064/841	1.26 (1.19 to 1.34)	
85–89	Women	775/678	1.14 (1.07 to 1.23)	0.40
	Men	313/258	1.21 (1.08 to 1.35)	
Test-positive angina				
45–54	Women	11/1	12.1 (6.06 to 21.7)	0.02
	Men	120/21	5.63 (4.71 to 6.74)	
55–64	Women	55/12	4.69 (3.60 to 6.11)	<0.001
	Men	229/95	2.40 (2.11 to 2.73)	
65–74	Women	221/88	2.50 (2.20 to 2.86)	<0.001
	Men	452/242	1.87 (1.70 to 2.05)	
75–84	Women	322/187	1.72 (1.54 to 1.92)	0.83
	Men	329/188	1.75 (1.57 to 1.95)	
85–89	Women	127/64	2.00 (1.68 to 2.37)	0.87
	Men	74/39	1.93 (1.54 to 2.42)	

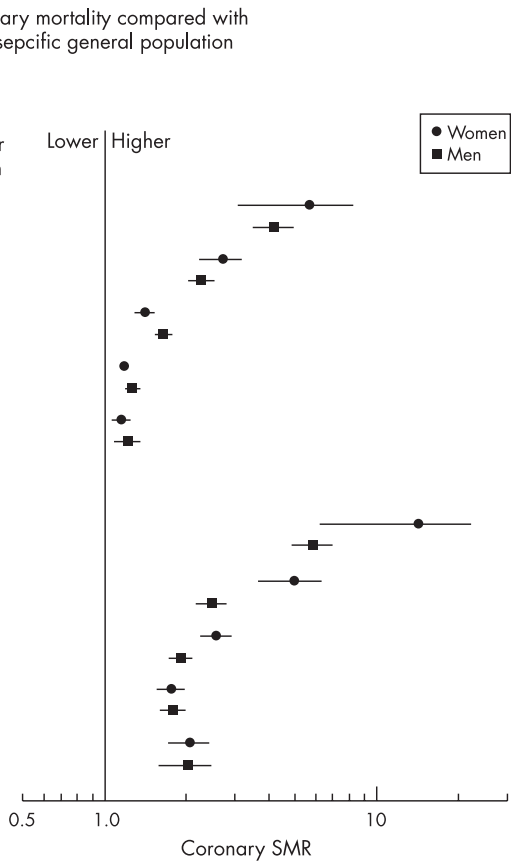

Figure 2 Prognosis of nitrate and test-positive angina: standardised mortality ratios (SMRs) for coronary heart disease by sex within age groups. Reprinted with permission from Hemingway H, McCallum A, Shipley M, *et al*. Incidence and prognostic implications of stable angina pectoris among women and men. *JAMA* 2006;**295**:1404–11. Copyright © 2007 American Medical Association.[3]

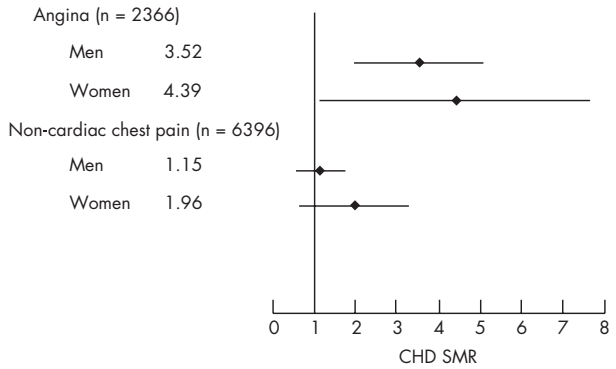

Figure 3 Standardised mortality ratios (SMRs) for coronary death in men and women aged <65 years attending rapid-access chest pain clinics with angina and non-cardiac chest pain.[20] CHD, coronary heart disease.

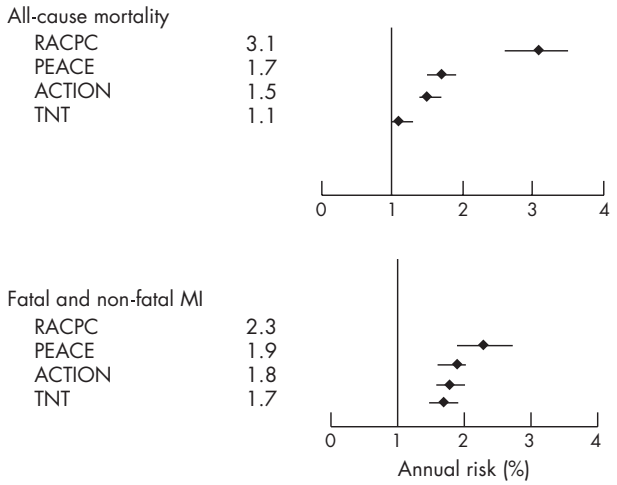

Figure 4 Prognosis of angina: annual rates of all-cause mortality and fatal/non-fatal myocardial infarction (MI) in patients attending rapid-access chest pain clinic (RACPC) compared with clinical trial patients. Data are rates (%) and 95% CI. ACTION, effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment; PEACE, Prevention of Events with Angiotensin Converting Enzyme inhibition; TNT, treating to new targets.

cases per year to the total 1996 Finnish population.[3] To capture all diagnosed cases of angina (a conservative measure of incidence), two mutually exclusive case definitions were used based on nitrate prescription and test positivity, yielding >90 000 and >27 000 cases, respectively. The incidence of stable angina as the first presentation of coronary disease was high (≈2 per 100 population per year), several folds higher than the incidence of non-fatal MI. Most estimates of incident MI do not consider MI occurring after angina, and thus are inflated estimates of first manifestation of coronary disease. A major finding of this large study is that the contemporary prognosis of patients with angina is not good and this is more consistent with the Framingham and Gothenburgh experience than that of the clinical trials. In the Finnish study, the estimated 10-year incidence of fatal and non-fatal MI >10% for women with nitrate angina and was still higher for men. Absolute risks were yet higher for test-positive angina. Poor prognosis was indicated in the standardised mortality ratios for CHD that were significantly increased across all age groups (fig 2).

Is the aetiology of stable angina different from other symptoms of coronary disease?

To understand the prognosis of angina, it is also necessary to understand its aetiology. Resolving the aggregate of CHD into different chronic and acute coronary syndromes could help identify specific causal factors, at a population level, for processes with notably different underlying biology. The Finnish study showed that the prognosis of angina is poor and also that the incidence of angina in both men and women is similar, with age-standardised annual incidence of 2.03 and 1.89, respectively, per 100 population. This lack of male excess contrasts with the male predominance in recent randomised trials. It also contrasts with the male predominance in (undifferentiated) MI, although this is less marked for unstable angina. These gender differences are important because they are likely to reflect aetiological differences between specific symptoms of coronary artery disease.

Is male sex a risk factor for stable angina prognosis?

Some risk factors may be prognostic but not aetiological, and vice versa. Although the Finnish data and the meta-analysis of healthy population studies suggest that being a man is not a risk factor for stable angina, it is clear that men are at a greater risk of subsequent MI. Existing cohort studies are too small to provide reliable estimates of sex differences in prognosis. To distinguish aetiology from prognosis, it is important to study the initial presentation of disease to avoid the potential for error through reverse causality. For example, numerous cohorts have assessed the association between baseline depression and risk of first MI, but there has been limited exploration of the possibility that the temporal sequence is stable angina, then depression and then MI.[18]

Large registers at initial referral to cardiologist

It is axiomatic that initial presentation of disease provides the end point for aetiological enquiry and the starting point for prognostic enquiry. Hitherto, large-scale studies of initial presentation with stable angina have been hampered by difficulties in identification and assessment of patients not admitted to hospital. This opportunity is now available for stable angina as a result of the rapid proliferation of chest pain clinics in nearly all hospitals in the UK. We have recently reported a multicentre study of 8762 patients with recent-onset chest pain, none of whom had a history of CHD.[19] In this ambulatory population, incident angina was diagnosed in 2366 patients, of whom 43% were women and 24% were of non-Caucasian ethnicity. Our data, like the Finnish study, showed that angina is not a low-risk diagnosis, the annual rate of coronary death and non-fatal MI being 2.3%, with an adjusted hazard ratio (95% CI) of 2.16 (1.40 to 3.34) compared with the 6396 patients with non-cardiac chest pain. We found no evidence of risk reduced to normal levels, standardised mortality ratios for coronary death in both men and women with incident angina being substantially higher than the general population (fig 3). Outcomes were also worse than those reported in recent trials that recruited contemporaneously with our own study. Most patients in these trials had a history of MI (table 1), emphasising the high-risk status of our incident angina cohort, none of whom had had previous coronary events (fig 4).

Prognosis of angina—why the disparity between registry and trial findings?

Understanding the higher risk for patients with incident angina seen in primary care and chest pain clinics compared with participants in recent treatment trials is important for improving the quality of care, and for advancing the hypotheses about causal pathways. Various factors are involved in this.

Table 1 Comparison of characteristics of patients with a history of myocardial infarction in different trials

	RACPC angina, 1996–2002 (n = 2366)	PEACE, 1996–2000 (n = 4132)	ACTION, 1996–1998 (n = 3840)	TNT, 1998–1999 (n = 5006)
Baseline risk factors				
Age	62 (11)	64 (8)	63.4 (9.3)	61 (9)
Females	43%	17%	21%	19%
Non-white ethnicity	24%	7% of cohort	2% of cohort	6%
Diabetes	17%	16%	14%	15%
Current smoker	23%	15%	17%	13%
Systolic blood pressure	147 (22)	133 (17)	138 (19)	131 (17)
Cardiac history				
Angina	100%	71%	92%	81%
MI	0%	56%	50%	58%
PTCA	0%	41%	20%–25%*	54%
CABG	0%	40%	—	47%
Drugs				
β Blockers	54%	60%	80%	—
Statins	28%	70%	62%	—
Aspirin	84%	91%	86%	—
Annual endpoint comparisons				
All-cause mortality (95% CI)†	3.1% (2.6 to 3.5)	1.7% (1.5 to 1.9)	1.5% (1.4 to 1.7)	1.1% (1.0 to 1.3)
Cardiovascular mortality (95% CI)†	1.8% (1.4 to 2.1)	0.8% (0.6 to 0.9)	0.8% (0.7 to 0.9)	—
CHD death and non-fatal MI (95% CI)†	2.3% (1.9 to 2.7)	1.9% (1.6 to 2.0)‡	1.8% (1.6 to 2.0) §	1.7% (1.5 to 1.9)

ACTION, effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment; CABG, coronary artery bypass graft; CHD, coronary heart disease; MI, myocardial infarction; PEACE, Prevention of Events with Angiotensin-Converting Enzyme inhibition; PTCA, percutaneous transluminal coronary angioplasty; RACPC, rapid-access chest pain clinic; TNT, Treating to New Targets.
*Annual incidence = total incidence of events/follow-up time.
†Range between those without and with a history of MI who had PTCA.
‡Figures are for annual cardiovascular death + nonfatal MI, so the actual figures for the endpoint are likely to be lower.
§Extracted from primary endpoint for safety (fatal + nonfatal cardiovascular events).

Resolving the spectrum of chronic coronary syndromes

An important reason for the prognostic differences between observational studies and clinical trials is that there are no common standards for defining, and reporting, the various chronic coronary syndromes that come under the single term stable angina. Professional bodies issue statements on the definitions of acute coronary syndromes but there have been none for stable angina. Thus, it is difficult to compare cases enrolled in one study with those in another. Until standardised case definitions for angina are agreed, prognostic assessments will remain variable and contradictory. Such case definitions need to consider:

- vasculopathy; ie, recognising that narrowing of large epicardial arteries is a sufficient but not a necessary determinant of ischaemic symptoms. Population-based studies of angina with coronary artery imaging have been lacking because of the risk and cost implications. With the advent of new imaging modalities, such as multislice CT, this may change. Certainly, chest pain may contribute to adverse outcomes independent of the presence and severity of epicardial coronary disease.[20 21] The role of microvascular disease is increasingly recognised as an important cause of ischaemia, particularly in women.[22]
- Symptom classification; recognising that angina is a symptom complex with poorly characterised measurement properties. Although laboratories standardise assays for biomarkers (eg, troponins), there are only a few data on the reliability of clinical history taking in angina. Because

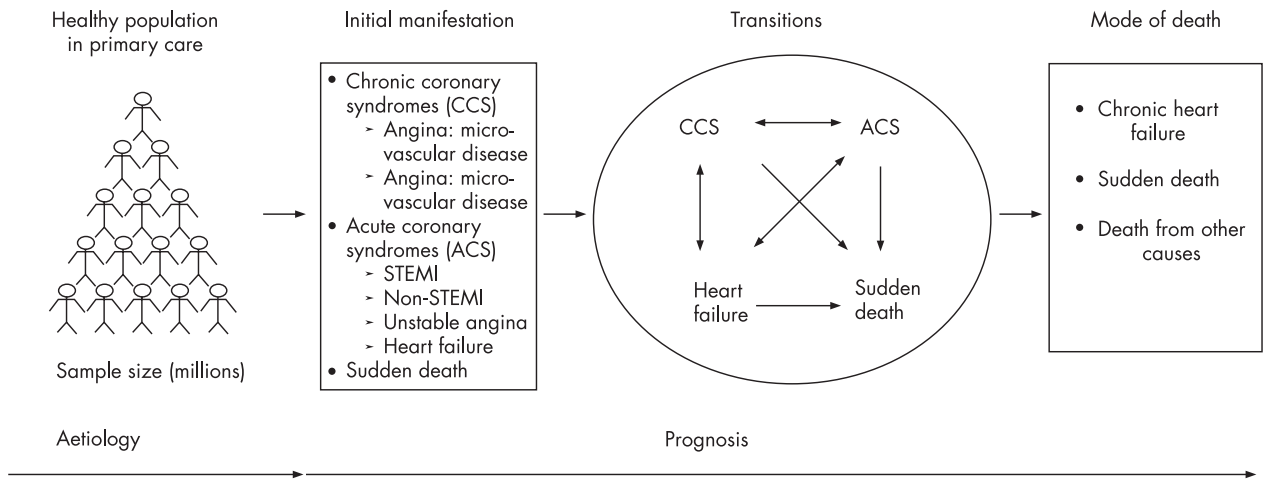

Figure 5 Understanding the aetiology and prognosis of coronary heart disease with large population studies resolving different phenotypic symptoms and their temporal relationships. STEMI, ST elevation myocardial infarction.

taking a patient history it is not standardised it is indicated in the imperfect agreement between the Rose Angina Questionnaire, widely used in general populations,[23 24] and clinical diagnoses. Ethnographic studies (C Somerville, personal communication, 2007) suggest that there is a complex process of negotiation between the doctor and the patient in assigning descriptors to chest pain in order to arrive at the diagnostic canon of typical, atypical and non-specific symptoms. These labels evoke different sets of diagnostic and prognostic assumptions, which are not always correct. Thus, it is increasingly recognised that the reassurance given to patients diagnosed with non-cardiac chest pain, or in whom coronary disease has been ruled out may be misplaced.[19] Prognostically important but previously neglected information may reside in the dialogue between the patient and the doctor. We need to know more about this lexomic to develop a more robust system of symptom classification.

- Longitudinal phenotype; recognising that angina is a chronic disorder, which may reveal itself to medical care episodically over time.[25] Most studies make no reference to the duration of angina, and prospective analyses of its clinical course from the date of first onset have not been undertaken. However, that opportunity now arises with the availability of complete longitudinal primary care records (eg, General Practice Research Database), with coding of each consultation. These records will provide us with the potential to increase our understanding of the aetiology and prognosis of angina in men and women.

Resolving the time sequence of different coronary morbidities

Participants in clinical trials have typically been survivors with late-stage disease at the time of enrolment. Most have had a history of MI and many have been revascularised. By contrast, patients in primary care presenting to chest pain clinics are at a much earlier stage of disease, with angina being its first symptom. Thus, despite stable symptoms, most participants in our multicentre chest pain clinic study were within 4 weeks and at most within 6 months of symptom onset, perhaps an indication of recent plaque instability that contributed towards their heightened risk compared with patients in trials. Studies are required with higher resolution of the temporal sequence between initial manifestations and subsequent transitions between different coronary morbidities to enhance our understanding of the natural history and prognosis of coronary disease (fig 5).

Resolving the spectrum of prognostic outcomes

The term prognosis tends to be elided with survival and all-cause mortality,[26] and with fatal events in apparent decline among certain groups with chronic angina, prognosis is generally regarded as improving. The non-fatal outcome of major interest is MI, but this undifferentiated end point embraces a range of phenotypes including ST elevation MI, non-ST elevation MI and unstable angina, which differ biologically and in terms of management and outcome. Future studies must distinguish between these coronary outcomes and must also examine symptom persistence, functional status, quality of life and utilities[27 28] to enhance the understanding of prognosis in its broadest sense.

Selection

Participants in clinical trials are highly selected according to predefined inclusion criteria, and hence it is difficult to generalise outcomes to patients with incident angina. This is emphasised by the under-representation of women and ethnic minorities in the trial populations, and by the tendency for trial patients to be free from important comorbidities.

Treatment

The trials show the importance of secondary prevention for risk reduction in angina. Information about treatment after the first chest pain clinic visit was unavailable in our study and we do not know if underuse contributed to the heightened risk of adverse outcomes compared with the clinical trials. Among our patients with angina, rates of aspirin and β-blocker treatments at the first visit were similar to those reported in the Euro Heart Survey,[29] although rates were lower for statins, >80% underwent further cardiological follow-up and we presume, therefore, that most came for treatment.

''The'' prognosis of angina

The significance of understanding the prognosis of angina lies in the observation that it is probably the most common initial symptomatic manifestation of coronary disease and represents an opportunity for early detection, risk stratification and treatment. Unqualified use of the definite article is currently premature with estimates of prognosis varying according to case definitions and the level in the population pyramid from which patients are selected. Nevertheless, it is at the base of the pyramid that patients with angina start their clinical journey, and in primary care and in chest pain clinics the prognosis may be considerably less favourable than for patients randomised in clinical trials. The external validity of trial findings—risk reduced to normal levels—should be judged in association with the study populations. Similar caveats apply to risk prediction models derived from trial populations.[30 31]

Future research

Larger population-based studies with finer resolution of coronary start points and end points are required to advance the understanding of the prognosis of angina. National registries of acute coronary syndromes provide well-characterised endpoint data and in England and Wales, the Myocardial Infarction National Audit Project, which returns data from all 230 hospitals, is already linked to hospital admission and mortality data. Linking the Myocardial Infarction National Audit Project to existing population studies, large longitudinal primary care datasets (eg, General Practice Research Database) and chest pain clinics offers the potential for large-scale study of initial presentation of angina. Such linkages have much to tell us about initial manifestations, progression and outcomes of angina and other manifestations of CHD (fig 5). Only in this way will we begin to understand the aetiological and prognostic differences between specific coronary disease phenotypes in women and men, a key challenge in the cardiological sciences. It is >80 years since MacKenzie's urgent call for understanding the prognosis of angina. It is time his call was met.

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